The old Schilling test as a necessary criterion at present for the diagnosis of food-cobalamin malabsorption (FCM) syndrome

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The inability to release vitamin B12 (Cbl) from its carrier proteins is characterized as food-cobalamin malabsorption (FCM) syndrome, the leading cause of Cbl deficiency in the elderly. This syndrome was first described by Doscherholmen in 1973 and well characterized by Carmel and Dawson in the 1990s. Several causes or "associated" disorders of Cbl malabsorption have been reported, the most common being age, atrophic gastritis, gastric disease associated with *Helicobacter pylori* infection, and the intake of proton pump inhibitors, H_2-receptor antagonists, or metformin.

In a number of recently published series, especially in elderly patients, FCM syndrome appears to be the leading cause of various Cbl deficiency aetiologies accounting for about 50%-60% of the cases, while pernicious anaemia (PA) is accounts for about 15%-30% of the cases. It should be noted that for measuring Cbl, various methods have been used: (chemiluminescence or radioassay) and consequent-

Table 1. *Tests employed to investigate the cause of Cbl deficiency*

Test	Rationale and advantage	Disadvantage
IF antibodies	Pathognomic for PA. High specificity is ~100%.	Relatively low sensitivity ~?70%. Methodologic diversity.
Pepsinogen	Mirrors gastric function; increases in gastric atrophy. High sensitivity.	Low specificity.
Gastrin	Mirrors gastric function; increases in gastric atrophy. Relatively high sensitivity.	Fasting sample needed. Low specificity.
Parietal cell antibodies	May be present in PA.	Low specificity.
Schilling test	Considered to be the gold standard as a functional test of Cbl absorption; measures absorption of free (I) or IF bound (II) Cbl by measurement of the amount of labeled Cbl excreted in the urine. High specificity if lack of IF is the cause of reduced Cbl absorption.	Requires administration of radioactive Cbl. Requires collection of 24h urine. Requires use of IF. False positive with reduced renal function. Decreasing availability.
Holotranscobalamin	Functional test of Cbl absorption; Measures absorption of free or IF-bound Cbl by measuring the increase in holotranscobalamin and thus whether IF can correct a reduced Cbl absorption. Expected to have a high specificity if lack of IF is the cause of reduced Cbl absorption	Requires availability of the holotranscobalamin assay. Needs further evaluation before introduction into routine clinical practice.
Gastroscopy with systematic biopsies	High specificity for atrophic gastritis. Taking biopsies.	Invasive method. Requires the cooperation of patient.

IF: intrinsic factor; PA: pernicious anaemia; Cbl: cobalamin, vitamin B12

Table 2. *A brief description of Schilling test*

Conditions	Stage 1 Oral radiolabeled free vitamin B12 [CN-(^{57}Co)Cbl] plus intramuscular unlabeled vitamin B12	Stage 2 CN-(^{57}Co)Cbl and IF
Normal (or FCM syndrome)	Normal absorption[1,2]	-
Lack of IF production (e.g. PA, atrophic gastritis total gastrectomy)	Reduced absorption	Normal absorption
Malabsorption	Reduced absorption	Reduced absorption

[1]A normal result shows at least 10% of the radiolabeled Cbl in the urine over the first 24h. [2]Reduced absorption using not free but protein-bound radiolabeled CN-(^{57}Co)Cbl (FCM syndrome).
IF: intrinsic factor; PA: pernicious anaemia; Cbl: cobalamin, vitamin B12; FCM: food-Cbl malabsorption.

ly there are different normal ranges and not a "gold standard". However, serum Cbl levels <200pg/mL are consistent with Cbl deficiency (specificity of 95% to 100%). Diagnostic criteria proposed for the FCM syndrome but unfortunately not still validated in the evidence-based medicine approach are the following three: a) low serum Cbl levels (<200pg/mL), b) normal "standard" Schilling test using free cyano-Cbl labeled with cobalt-57 or abnormal "modified" Schilling test using protein-bound radioactive cyano-Cbl, and c) absence of dietary Cbl deficiency with an intake of Cbl of equal or at least more than 2.5 to 5μg per day. Thus, Schilling tests (standard and modified) are the "gold standard" to establish the diagnosis of FCM syndrome referring to all Cbl deficiencies that are related to the pre-absorption of Cbl steps. Because these tests are not currently available in clinical practice, since 2003, FCM syndrome remains a diagnosis of exclusion. Analytically, once Cbl deficiency has been documented (serum levels of Cbl <200pg/mL and total homocystein >15μmol/L), the first step towards aetiological diagnosis is to rule out insufficient nutritional Cbl intake or intestinal malabsorption by taking a thorough food anamnesis and searching for other clinical or biological signs of malnutrition or malabsorption. The next step aims to eliminate PA, the main differential diagnosis of FCM, by searching for anti-intrinsic factor antibodies and anti-gastric parietal cell antibodies, and performing a gastroscopy with systematic biopsies so as to detect auto-immune atrophic funditis. After exclusion of PA diagnosis, the FCM syndrome arises as the most likely cause of Cbl deficiency. It's important to note that this "deductive elimination" FCM diagnosis process has not been validated in an evidence based medicine approach.

Considering that Schilling test has a high specificity for PA and also examines both gastric and intestinal stage of Cbl absorption, such as the release of Cbl from its carrier proteins, as compared to other diagnostic procedures, restoration of Schilling test in the clinical setting is necessary. Tests employed to investigate the cause of Cbl deficiency and a brief description of Schilling test, are found in Tables 1 and 2.